Dose dense EC-Paclitaxel (Breast) (Epirubicin and Cyclophosphamide and Paclitaxel)

Indication
Adjuvant or neo-adjuvant treatment for high risk early stage and locally advanced breast cancer.

ICD-10 codes
Codes with a prefix C50

Regimen details
Cycles 1-4 EC

Day	Drug	Dose	Route
1	Epirubicin	90mg/m^2	IV bolus
1	Cyclophosphamide	600mg/m^2	IV bolus

Cycles 5-8 Paclitaxel
2 weekly

Day	Drug	Dose	Route
1	Paclitaxel	175mg/m^2	IV infusion

Weekly (on a 21 day cycle)

Day	Drug	Dose	Route
1, 8, 15	Paclitaxel	80mg/m^2	IV infusion

Cycle frequency
EC and 2 weekly paclitaxel: 14 days (with GCSF support)
Weekly paclitaxel: 21 days

Number of cycles
Maximum of 8 cycles (4 x EC followed by 4 x paclitaxel)
Note: scheduling can also be reversed to give the paclitaxel cycles prior to the EC.

Administration
Epirubicin and cyclophosphamide are administered by slow IV bolus into the arm of a fast running drip of sodium chloride 0.9%. Cyclophosphamide may also be given as an IV infusion in 250-500mL sodium chloride 0.9% over 30 minutes.

Paclitaxel is administered as an IV infusion in 250-500mL PVC free sodium chloride 0.9% via a 0.22 in line filter over 1-3 hours.

Patients should be observed closely for hypersensitivity reactions, particularly during the first and second infusions.

Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of paclitaxel and therefore facilities for the treatment of hypotension and bronchospasm must be available.

If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require discontinuation of therapy. The infusion may be temporarily interrupted and when symptoms improve re-started at a slower infusion rate. Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of paclitaxel and appropriate therapy.

Pre-medication

EC cycles: none usually required
Paclitaxel cycles: A corticosteroid and antihistamine should be given 30 minutes prior to the infusion.
For example:
Dexamethasone 16-20mg IV (8mg if paclitaxel administered weekly)
Chlorphenamine 10mg IV

Emetogenicity

EC cycles: moderate - high emetic potential
Paclitaxel cycles: moderate emetic potential

Additional supportive medication

GCSF must be prescribed for EC cycles and 2-weekly paclitaxel cycles. GCSF is not usually required if weekly paclitaxel is used.
Mouthwashes as per local policy
Proton-pump inhibitor if required
Loperamide if required.

Extravasation

Epirubicin and paclitaxel are vesicant (Group 5)
Cyclophosphamide is neutral (Group 1)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days

ECHO or MUGA if significant cardiac history or previous anthracycline treatment.

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	48 hours (or within 24 hours of each weekly paclitaxel dose)
U+E (including creatinine)	96 hours
LFTs	96 hours

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
Creatinine Clearance (CrCl)	> 20 mL/min
Bilirubin	≤ 1.0 ULN
AST/ALT	≤ 2.0 x ULN (see below for further information)
Alkaline Phosphatase	≤ 2.5 x ULN

Dose modifications

- **Haematological toxicity**

If neutrophils <1.0 x 10^9/L and/or platelets <100 x 10^9/L delay 1 week or until recovery. If more than one delay in EC change to 3 weekly cycle. For paclitaxel consider changing to weekly dosing.
If febrile neutropenia despite GCSF or neutrophils < 0.5 x 10^9/L for more than 1 week consider reducing doses of all drugs to 80% for future cycles.

- **Renal impairment**

CrCl (mL/min)	**Cyclophosphamide dose**
> 20	100%
10-20	75%
<10	50%

There is no data available on the use of epirubicin in severe renal impairment. Consider dose reduction if CrCl <10mL/min (consultant decision).

Paclitaxel: no dose modifications recommended.

- **Hepatic impairment**

EC cycles:

Bilirubin (x ULN)		**AST/ALT** (x ULN)		**Alkaline phosphatase** (xULN)	**Epirubicin dose**	**Cyclophosphamide dose**
< 1.5	and	≤ 2.0	and	≤ 2.5	100%	100%
1.5 - < 3	or	> 2.0 -3.5	or	> 2.5 - <5	50%	100%*
≥3 - 5	or	> 3.5	and	5-10	25%	Consider dose reduction (discuss with consultant)
> 5			or	> 10	Omit	Contraindicated

*Cyclophosphamide is not recommended if bilirubin > 1.5 x ULN or AST/ALT > 3 x ULN (consultant decision).

2-weekly Paclitaxel cycles:

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Paclitaxel dose**
<ULN	and	<5	100%
1-1.5	and		135mg/m^2
1.5-2.5	and		75mg/m^2
2.5-4	and		50mg/m^2
> 4	or	≥5	Not recommended (consultant decision)

Weekly paclitaxel cycles:
Paclitaxel is not recommended in severe hepatic impairment. If bilirubin < 1.5 x ULN and AST/ALT < 5 x ULN proceed with 100% dose. For more severe hepatic impairment, treatment may only proceed on consultant's decision, at a reduced dose with weekly monitoring of LFTs.

- **Other toxicities**

For grade 3 or 4 mucositis/stomatitis – delay until resolved to ≤ grade 1 and reduce epirubicin to 80% dose.

For grade 2 neuropathy – reduce paclitaxel to 80% dose. If persists consider further dose reduction.

Any other grade 3 or 4 toxicity- discuss with consultant.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Secondary malignancy
Myelosuppression
Infusion related reactions
Anaphylaxis
Teratogenicity
Infertility/Early menopause
Cardiotoxicity
Peripheral neuropathy

- **Frequently occurring side effects**

Diarrhoea, constipation
Fatigue
Nausea and vomiting
Myelosuppression
Stomatitis and mucositis
Arthralgia and myalgia
Alopecia

- **Other side effects**

Fluid retention
Red urine (for 24 hours post epirubicin)
Deranged liver function
Phlebitis
Skin toxicity
Nail changes
Taste disturbances
Bladder irritation

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.
Phenytoin: requires close monitoring if using concurrently.

Cyclophosphamide:
Amiodarone: increased risk of pulmonary fibrosis – avoid if possible
Azathioprine: increased risk of hepatotoxicity
Clozapine: increased risk of agranulocytosis – avoid concomitant use
CYP2B6 and CYP3A4 inhibitors (Nevirapin, Ritonavir): co-administration may reduce the efficacy of cyclophosphamide
Digoxin tablets: reduced absorption – give as liquid form
Indapamide: prolonged leucopenia is possible - avoid
Itraconazole: may increase adverse effects of cyclophosphamide
Grapefruit juice: decreased or delayed activation of cyclophosphamide. Patients should be advised to avoid grapefruit juice for 48 hours before and on day of cyclophosphamide dose.

Paclitaxel:
Clozapine: increased risk of agranulocytosis
Paclitaxel is a CYP 2C8/9 and CYP 3A4 substrate. Drug levels may be increased by inhibitors of these enzymes and decreased by inducers of these enzymes.

Additional comments

Epirubicin has a life time maximum cumulative dose of 900mg/m^2

References

- Summary of Product Characteristics Epirubicin (Medac) accessed 23 November 2023 via www.medicines.org.uk
- Summary of Product Characteristics Cyclophosphamide (Sandoz) accessed 23 November 2023 via www.medicines.org.uk
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- Del Maestro, L., et al. Fluorouracil and Dose Dense Chemotherapy in adjuvant treatment of patients with early stage breast cancer. Lancet 2015. 385. 1863-1872
- EBCTCG. Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials, Lancet 2019. 393. 1440-52

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Date: November 2023